May 28, 2002

VETERINARY SERVICES MEMORANDUM NO. 800.203

Subject: General Licensing Considerations: Antigen Interference

To: Veterinary Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

This memorandum provides guidance in the evaluation of polyvalent biological products for the possibility of interference by one antigen on the immune response to another antigen.

II. BACKGROUND

The products covered by this memorandum are vaccines and similar prophylactic immunobiologicals, such as bacterins or toxoids, which contain antigens intended to actively stimulate an immune response in the recipient. Antigenic fractions with previously established efficacy in licensed products may be combined to form a new polyvalent product. It must be verified that the efficacy of each fraction has not been compromised in the new product compared to the existing products.

III. DEFINITIONS

A. Antigen Interference

Antigen interference is the reduction of the expected immune response to one antigen by the presence of another antigen in the same product.

B. Excessive Interference

Interference is excessive when there is reason to believe the product's efficacy against disease has been limited by the reduction of the immune response due to interference.

C. Fraction

A fraction of a prophylactic immunobiological product refers to a component antigen (organism) and the form in which it appears (e.g., modified live, inactivated, subunit, toxoid, vectored, etc.).

IV. GUIDELINES

Material submitted for licensing new products formed from combinations of licensed products must include information supporting the absence of excessive antigen interference. Support for the absence of excessive interference may be done in one of several ways.

A. Efficacy Study

A satisfactory efficacy study conducted with the new product verifies the absence of excessive interference on the vaccine antigen that was challenged. Efficacy studies may be conducted for any new product and must be conducted for the following:

1. *Avian Products* - Conduct an efficacy study for each fraction of new polyvalent products intended for use in poultry.

2. *Mammalian Products* - Conduct an efficacy study for each fraction of new polyvalent products intended for use in mammals if the new product differs significantly from the existing products in composition, production methods, or recommended vaccination regimen.

B. Existing Information

Submit convincing substantive information documenting the absence of excessive interference. Such information may include previous studies or documented experience with the fractions comprising the new product.

C. Potency Test

Potency tests which are considered particularly convincing measures of a fraction's protective efficacy may be sufficient support for the absence of excessive interference. Acceptable potency tests have been limited to the *in vivo* tests found in the Standard Requirements for *Leptospira* species, *Clostridium* species, and the equine viral encephalitides (Code of Federal Regulations, Title 9, Part 113).

D. Comparative Serology

Conduct a study in the target species comparing the geometric mean serum titer (GMT) between a group vaccinated with the new product and a group vaccinated with the existing product. The absence of excessive interference would be supported if the GMTs were equivalent. In most cases, the antibody response measured by the assay need not have been conclusively linked to challenge resistance.

1. *Methods* -

a. Design. Design the study for data analysis and statistical inference by accepted equivalence methodology.

b. Equivalence. Two values are equivalent if they differ by less than an amount which is considered meaningful in a clinical or practical sense. The range within which two values are considered equivalent is termed the equivalence margin.

c. Serial potency. The serials of the new and existing products used in the study should be formulated to contain the same amount of the fraction under investigation. If possible, formulate both products from the same bulk lots.

2. *Criteria* -

a. Noninferiority. It is sufficient to demonstrate the serological noninferiority of the new product. Serological noninferiority means that the expected GMT of the group vaccinated with the new product is not lower than the expected GMT of the group vaccinated with the existing product by more than the equivalence margin. It may be higher by any amount.

b. Margin. Protocols proposing serological equivalence studies must explicitly state the criterion determining the noninferiority margin. Use the 70% criterion, which aims to show that the new product GMT is at least 70% of the existing product GMT, unless another criterion is justified. A 70% titer ratio corresponds to a difference of about one half of a twofold dilution in a serial dilution assay. The 70% criterion does not necessarily apply to applications other than antigen interference studies.

c. Confidence. For serological noninferiority studies, use a 0.075 level of significance. For example, if comparing a confidence interval to the

equivalence margin, use an 85% confidence interval, and, for noninferiority, compare only the lower ends.

3. *Field Studies* - The precision of serum titrations in some cases may require that a serological equivalence study include more subjects than available for an experimental study. Serum derived from appropriately designed field studies may be used to study serological equivalence. For example, subjects in a field safety trial may be randomized to new and existing products. While such subjects would not necessarily be seronegative, they would emulate the target population as well as the rest of the field safety study sample.

/s/ W. Ron DeHaven

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